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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07K 5/06, 14/81, A61K 38/55</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/11129</b> <b>(43) International Publication Date:</b> 19 March 1998 (19.03.98)
<b>(21) International Application Number:</b> PCT/US97/16157 <b>(22) International Filing Date:</b> 12 September 1997 (12.09.97)  <b>(30) Priority Data:</b> 60/026,011 12 September 1996 (12.09.96) US 08/767,175 16 December 1996 (16.12.96) US  <b>(71) Applicant:</b> IDUN PHARMACEUTICALS, INCORPORATED [US/US]; Suite 300, 11085 North Torrey Pines Road, La Jolla, CA 92037 (US).  <b>(72) Inventors:</b> KARANEWSKY, Donald, S.; 1797 Continental Lane, Escondido, CA 92024 (US). BAI, Xu; 3357 Avenida Nieve, Carlsbad, CA 92009 (US).  <b>(74) Agents:</b> STEINHARDT, Paul, C. et al.; Campbell and Flores LLP, Suite 700, 4370 La Jolla Village Drive, San Diego, CA 92122 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> C-TERMINAL MODIFIED (N-SUBSTITUTED)-2-INDOLYL DIPEPTIDES AS INHIBITORS OF THE ICE/ced-3 FAMILY OF CYSTEINE PROTEASES		
<b>(57) Abstract</b>  This invention is directed to novel (N-substituted)indole ICE/ced-3-inhibitor compounds. The invention is also directed to pharmaceutical compositions of such indole compounds, plus the use of such compositions in the treatment of patients suffering inflammatory, autoimmune and neurodegenerative diseases, and for the prevention of ischemic injury.		

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C-TERMINAL MODIFIED (N-SUBSTITUTED)-2-INDOLYL  
DIPEPTIDES AS INHIBITORS OF THE ICE/ced-3 FAMILY  
OF CYSTEINE PROTEASES

BACKGROUND OF THE INVENTION

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Field of the Invention

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1 $\beta$  converting enzyme and related proteases ("ICE/ced-3 family of cysteine proteases"). This invention also relates to pharmaceutical compositions comprising these compounds and to methods of using such pharmaceutical compositions. The compounds, pharmaceutical compositions and methods of this invention are particularly well suited for inhibiting the protease activity of the ICE/ced-3 family and consequently, may be advantageously used as agents against interleukin-1 ("IL-1") mediated diseases, including inflammatory diseases, autoimmune diseases and neurodegenerative diseases and for inhibiting unwanted apoptosis in various disease states such as ischemic injury to the heart (e.g., myocardial infarction), brain (e.g., stroke), and kidney (e.g., ischemic kidney disease).

Background Information

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and neutrophil

activation. Oppenheim, J.H. et al., Immunology Today, 7:45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. IL-1 is predominantly produced by  
5 peripheral blood monocytes as part of the inflammatory response. Mosely, B.S. et al., Proc. Nat. Acad. Sci., 84:4572-4576 (1987); Lonnemann, G. et al., Eur. J. Immunol., 19:1531-1536 (1989).

IL-1 $\beta$  is synthesized as a biologically inactive  
10 precursor, proIL-1 $\beta$ . ProIL-1 $\beta$  is cleaved by a cysteine protease called interleukin-1 $\beta$  converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R. et al., J. Biol. Chem.,  
15 265:14526-14528 (1992); A.D. Howard et al., J. Immunol., 147:2964-2969 (1991).

ICE is a cysteine protease localized primarily in monocytes. In addition to promoting the pro-inflammatory and immunoregulatory properties of  
20 IL-1 $\beta$ , ICE, and particularly its homologues, also appear to be involved in the regulation of cell death or apoptosis. Yuan, J. et al., Cell, 75:641-652 (1993); Miura, M. et al., Cell, 75:653-660 (1993); Nett-Giordalisi, M.A. et al., J. Cell Biochem., 17B:117  
25 (1993). In particular, ICE or ICE/ced-3 homologues are thought to be associated with the regulation of apoptosis in neurogenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259:760-762 (1993); Gagliardini, V. et al., Science,  
30 263:826-828 (1994).

Thus, disease states in which inhibitors of the ICE/ced-3 family of cysteine proteases may be useful as

therapeutic agents include: infectious diseases, such as meningitis and salpingitis; septic shock, respiratory diseases; inflammatory conditions, such as arthritis, cholangitis, colitis, encephalitis, endocervicitis, hepatitis, pancreatitis and reperfusion injury, ischemic diseases such as the myocardial infarction, stroke and ischemic kidney disease; immune-based diseases, such as hypersensitivity; auto-immune diseases, such as multiple sclerosis; bone diseases; and certain neurodegenerative diseases, such as Alzheimer's and Parkinson's disease.

ICE/ced-3 inhibitors represent a class of compounds useful for the control of the above-listed disease states. Peptide and peptidyl inhibitors of ICE have been described. However, such inhibitors have been typically characterized by undesirable pharmacologic properties, such as poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. These undesirable properties have hampered their development into effective drugs.

Accordingly, the need exists for compounds that can effectively inhibit the action of the ICE/ced-3 family of proteases, for use as agents for preventing unwanted apoptosis and for treating chronic and acute forms of IL-1 mediated diseases, such as inflammatory, autoimmune or neurodegenerative diseases. The present invention satisfies this need and provide related advantages as well.

**SUMMARY OF THE INVENTION**

One aspect of the instant invention is the compounds of Formula 1, set forth below.

5 A further aspect of the instant invention is pharmaceutical compositions comprising a compound of the above Formula 1 and a pharmaceutically-acceptable carrier therefor.

Other aspects of this invention involve a method for treating an autoimmune disease, an  
10 inflammatory disease, or a neurodegenerative disease comprising administering an effective amount of a pharmaceutical composition discussed above to a patient in need of such treatment.

Another aspect of the instant invention is a  
15 method of preventing ischemic injury to a patient suffering from a disease associated with ischemic injury comprising administering an effective amount of the pharmaceutical composition discussed above to a patient in need of such treatment.

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**BRIEF DESCRIPTION OF THE DRAWINGS**

**Figure 1** sets forth the activity of the compounds in Formula A in inhibiting the activity of ICE and CPP32 enzymes.

**Figure 2** illustrates the activity of the  
25 compounds in Formula B regarding recombinant ICE, CPP32, Mch2 and Mch5 enzymes.

**Figure 3** illustrates the activity of the compounds in Formula C regarding recombinant ICE, CPP32, Mch2 and Mch5 enzymes.

**DETAILED DESCRIPTION**

The compounds of this invention incorporate an

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